

In the Claims

1. (Currently Amended) A pharmaceutical composition ~~active on that~~ inhibits angiogenesis comprising as active agent at least one substance selected from the group consisting of a molecule comprising a nucleic acid which inhibits expression of a peptide chain encoded by nucleic acid residues 1022 to 4747 shown in SEQ ID NO: 28 ~~nucleic acid molecule of a gene coding for protein IRS-1, and a fragments thereof~~ of said molecule comprising at least 12 contiguous nucleotides which inhibits expression of a peptide chain encoded by nucleic acid residues 1022 to 4747 shown in SEQ ID NO: 28, and a pharmaceutically acceptable vehicle.

2. (Cancelled)

3. (Currently Amended) The pharmaceutical composition according to claim 1, wherein the active agent ~~molecule which inhibits expression of a nucleic acid molecule of a gene coding for protein IRS-1~~ is an antisense nucleic acid sequence comprising at least twelve contiguous nucleotides complementary to the ~~of a coding strand region~~ of SEQ ID NO. 28 ~~comprising at least twelve contiguous nucleotides or a sequence capable of hybridizing under strict conditions with one of the sequence SEQ ID NO. 2, 3 or 4, or with a fragment thereof of at least 12 contiguous nucleotides.~~

4. (Currently Amended) The pharmaceutical composition according to claim 1, wherein the active agent ~~molecule which inhibits expression of a nucleic acid molecule of a gene coding for protein IRS-1~~ is selected from the group consisting of the nucleic acid sequences shown in SEQ ID NO. 2, SEQ ID NO. 3, SEQ ID NO. 4, SEQ ID NO. 5, SEQ ID NO. 6, SEQ ID NO. 7, SEQ ID NO. 8, SEQ ID NO. 9, SEQ ID NO. 10, SEQ ID NO. 11, SEQ ID NO. 12, SEQ ID NO. 13, SEQ ID NO. 14, SEQ ID NO. 15, SEQ ID NO. 16, SEQ ID NO. 17, SEQ ID NO. 18, SEQ ID NO. 19, SEQ ID NO. 20, SEQ ID NO. 21, SEQ ID NO. 22, and SEQ ID NO. 23 and or a fragments of these nucleic acid sequences thereof comprising at least twelve

~~contiguous nucleotides or a sequence capable of hybridizing under strict conditions with one of the sequence SEQ ID NO. 2, 3 or 4, or with a fragment thereof of at least 12 contiguous nucleotides.~~

5. (Cancelled)

6. (Previously Presented) The pharmaceutical composition according to claim 4, which contains about 0.001 mg to about 50 mg of active agent and is in a form capable of subcutaneous, intramuscular, intravenous or transdermal administration.

7. (Withdrawn) A method of inhibiting angiogenesis comprising administering a pharmaceutically effective amount of a molecule which inhibits expression of a nucleic acid molecule of a gene coding for protein IRS-1.

8. (Withdrawn) The method according to claim 7, wherein the active agent is at least one nucleotide sequence selected from among the group consisting of SEQ ID No. 2, SEQ ID No. 3, SEQ ID No. 4, SEQ ID No. 5, SEQ ID No. 6, SEQ ID NO. 7, SEQ ID NO. 8, SEQ ID NO. 9, SEQ ID NO. 10, SEQ ID NO. 11, SEQ ID NO. 12, SEQ ID NO. 13, SEQ ID NO. 14, SEQ ID NO. 15, SEQ ID NO. 16, SEQ ID NO. 17, SEQ ID NO. 18, SEQ ID NO. 19, SEQ ID NO. 20, SEQ ID NO. 21, SEQ ID NO. 22, SEQ ID NO. 23 and SEQ ID NO. 28.

9. (Withdrawn) The method according to claim 7, wherein the molecule which inhibits expression of a nucleic acid molecule coding for protein IRS-1 is an antisense sequence of a coding region of SEQ ID NO. 28 comprising at least twelve contiguous nucleotides or derivatives thereof.

10. (Withdrawn) The method according to claim 7, wherein the molecule which inhibits expression of a nucleic acid molecule of a gene coding for protein IRS-1 is selected from the group consisting of SEQ ID NO. 2, SEQ ID NO. 3, SEQ ID NO. 4, SEQ ID NO. 5, SEQ ID NO. 6, SEQ ID NO. 7, SEQ ID NO. 8, SEQ ID NO. 9, SEQ ID NO. 10, SEQ ID NO. 11, SEQ

ID NO. 12, SEQ ID NO. 13, SEQ ID NO. 14, SEQ ID NO. 15, SEQ ID NO. 16, SEQ ID NO. 17, SEQ ID NO. 18, SEQ ID NO. 19, SEQ ID NO. 20, SEQ ID NO. 21, SEQ ID NO. 22 and SEQ ID NO. 23 or a fragment thereof comprising at least twelve contiguous nucleotides or derivatives thereof.

11. (Withdrawn) The method according to claim 7, which contains about 0.001 mg to about 50 mg of active agent and is in a form capable of subcutaneous, intramuscular, intravenous or transdermal administration.

12. (Withdrawn) A method of treating retinopathy, rheumatoid arthritis, Crohn's disease, atherosclerosis, hyperstimulation of the ovary, psoriasis, endometritis associated with neovascularization, restenosis due to balloon angioplasty, tissue superproduction due to cicatrization, peripheral vascular disease, hypertension, vascular inflammation, Raynaud's disease and Raynaud's phenomena, aneurysm, arterial restenosis, thrombophlebitis, lymphangitis, lymphedema, tissue cicatrization and repair, ischemia, angina, myocardial infarction, chronic heart disease, congestive heart failure, age-related macular degeneration or osteoporosis comprising administering a pharmaceutically effective amount of an active agent comprising at least one substance selected from the group consisting of (i) a molecule selected from a nucleic acid molecule of a gene coding for protein IRS-1 and a fragment thereof and (ii) a molecule which inhibits expression of a nucleic acid molecule according to (i).

13. (Withdrawn) The method according to claim 12, wherein the active agent is at least one nucleotide sequence selected from among the group consisting of SEQ ID NO. 2, SEQ ID NO. 3, SEQ ID NO. 4, SEQ ID NO. 5, SEQ ID NO. 6, SEQ ID NO. 7, SEQ ID NO. 8, SEQ ID NO. 9, SEQ ID NO. 10, SEQ ID NO. 11, SEQ ID NO. 12, SEQ ID NO. 13, SEQ ID NO. 14, SEQ ID NO. 15, SEQ ID NO. 16, SEQ ID NO. 17, SEQ ID NO. 18, SEQ ID NO. 19, SEQ ID NO. 20, SEQ ID NO. 21, SEQ ID NO. 22, SEQ ID NO. 23 and SEQ ID NO. 28.

14. (Withdrawn) The method according to claim 12, wherein the molecule which inhibits expression of a nucleic acid molecule coding for protein IRS-1 is an antisense sequence of a coding region of SEQ ID NO. 28 comprising at least twelve contiguous nucleotides or derivatives thereof.

15. (Withdrawn) The method according to claim 12, wherein the molecule which inhibits expression of a nucleic acid molecule of a gene coding for protein IRS-1 is selected from the group consisting of SEQ ID NO. 2, SEQ ID NO. 3, SEQ ID NO. 4, SEQ ID NO. 5, SEQ ID NO. 6, SEQ ID NO. 7, SEQ ID NO. 8, SEQ ID NO. 9, SEQ ID NO. 10, SEQ ID NO. 11, SEQ ID NO. 12, SEQ ID NO. 13, SEQ ID NO. 14, SEQ ID NO. 15, SEQ ID NO. 16, SEQ ID NO. 17, SEQ ID NO. 18, SEQ ID NO. 19, SEQ ID NO. 20, SEQ ID NO. 21, SEQ ID NO. 22 and SEQ ID NO. 23 or a fragment thereof comprising at least twelve contiguous nucleotides or derivatives thereof.

16. (Withdrawn) The method according to claim 12, which contains about 0.001 mg to about 50 mg of active agent and is in a form capable of subcutaneous, intramuscular, intravenous or transdermal administration.

17. (Withdrawn) A method of diagnosing pathologies linked to angiogenesis comprising:

- contacting a composition containing an active agent including at least one substance selected from the group consisting of (i) a nucleic acid molecule of a gene coding for protein IRS-1, a complementary sequence or a fragment thereof and (ii) a molecule which inhibits expression of a nucleic acid molecule according to (i) and target cells in a condition sufficient to permit inhibition of IRS-1 gene expression;
- measuring expression of the IRS-1 protein by the cells; and

- comparing expression of the protein measured before and after hybridization to measure inhibition of the expression.

18. (Withdrawn) The method according to claim 17, wherein the pathologies are selected from the group consisting of retinopathies, rheumatoid arthritis, Crohn's disease, atherosclerosis, hyperstimulation of the ovary, psoriasis, endometritis associated with neovascularization, restenosis due to balloon angioplasty, tissue overproduction due to cicatrization, peripheral vascular disease, hypertension, vascular inflammation, Raynaud's disease, Raynaud's phenomena, aneurysm, arterial restenosis, thrombophlebitis, lymphangitis, lymphedema, tissue cicatrization and repair, ischemia, angina, myocardial infarction, chronic heart disease, congestive heart failure, age-related macular degeneration and osteoporosis.

19. (Currently Amended) An isolated antisense nucleic acid molecule ~~comprising a~~ consisting essentially of a nucleotide sequence selected from the group consisting of SEQ ID NO. 2, SEQ ID NO. 3, SEQ ID NO. 4, SEQ ID NO. 5, SEQ ID NO. 6, SEQ ID NO. 7, SEQ ID NO. 8, SEQ ID NO. 9, SEQ ID NO. 10, SEQ ID NO. 11, SEQ ID NO. 12, SEQ ID NO. 13, SEQ ID NO. 14, SEQ ID NO. 15, SEQ ID NO. 16, SEQ ID NO. 17, SEQ ID NO. 18, SEQ ID NO. 19, SEQ ID NO. 20, SEQ ID NO. 21, SEQ ID NO. 22 and SEQ ID NO. 23.

20. (Currently Amended) A pharmaceutical composition comprising the isolated antisense nucleic acid molecule of claim 19 and a pharmaceutically acceptable vehicle.

21. (Withdrawn) A method of inhibiting angiogenesis comprising the step of administering to living cells the pharmaceutical composition of claim 20.

22. (Withdrawn) The method of claim 21, wherein a pathology linked to angiogenesis is treated.

23. (Withdrawn) The method of claim 22, wherein the pathology linked to angiogenesis is selected from the group consisting of retinopathy, rheumatoid arthritis, Crohn's

disease, atherosclerosis, hyperstimulation of the ovary, psoriasis, endometritis associated with neovascularization, restenosis due to balloon angioplasty, tissue superproduction due to cicatrization, peripheral vascular disease, hypertension, vascular inflammation, Raynaud's disease, Raynaud's phenomena, aneurysm, arterial restenosis, thrombophlebitis, lymphangitis, lymphedema, tissue cicatrization and repair, ischemia, angina, myocardial infarction, chronic heart disease, congestive heart failure, age-related macular degeneration and osteoporosis:

24. (Withdrawn) A method of diagnosing a pathology linked to angio-genesis comprising the steps of:

contacting a composition containing the isolated nucleic acid molecule of claim 19 and target cells in a condition sufficient to permit inhibition of IRS-1 gene expression;

measuring expression of the IRS-1 protein by the target cells; and

comparing expression of the IRS-1 protein measured in the target cells before and after contact with the isolated nucleic acid molecule to measure inhibition of IRS-1 expression.

25. (Withdrawn) The method of claim 24, wherein the pathology linked to angiogenesis is selected from the group consisting of retinopathy, rheumatoid arthritis, Crohn's disease, atherosclerosis, hyperstimulation of the ovary, psoriasis, endometritis associated with neovascularization, restenosis due to balloon angioplasty, tissue superproduction due to cicatrization, peripheral vascular disease, hypertension, vascular inflammation, Raynaud's disease and Raynaud's phenomena, aneurysm, arterial restenosis, thrombophlebitis, lymphangitis, lymphedema, tissue cicatrization and repair, ischemia, angina, myocardial infarction, chronic heart disease, congestive heart failure, age-related macular degeneration and osteoporosis.

26. (Currently Amended) The pharmaceutical composition of claim 1, wherein the active agent molecule which inhibits expression of a nucleic acid molecule of a gene coding for protein IRS-1 is the nucleotide sequence shown in SEQ ID NO. 3 or a fragment thereof

comprising at least 12 contiguous nucleotides shown in SEQ ID NO: 3 ~~or a sequence capable of hybridizing under strict conditions with the sequence SEQ ID NO. 3, or with a fragment thereof of at least 12 contiguous nucleotides.~~

27. (Currently Amended) The pharmaceutical composition of claim 1, wherein the active agent molecule ~~which inhibits expression of a nucleic acid molecule of a gene coding for protein IRS-1~~ is the nucleotide sequence shown in SEQ ID NO. 4 or a fragment thereof comprising at least 12 contiguous nucleotides shown in SEQ ID NO: 4 ~~or a sequence capable of hybridizing under strict conditions with the sequence SEQ ID NO. 4, or with a fragment thereof of at least 12 contiguous nucleotides.~~